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EXAMINER	
ALLEN, M	
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DATE MAILED: 06/28/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

07/28
08/28
09/28

☑ This application has been examined ☑ Responsive to communication filed on 1/16/95 ☑ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 26, 31, 36, 42-55, 75-87, 89-94 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☑ Claims 1-25, 27, 30, 32-33, 37-41, 56-74 have been cancelled.
3. ☑ Claims 88 are allowed.
4. ☑ Claims 26, 31, 36, 42-55, 75-87, 89-94 are rejected.
5. ☑ Claims 28-29, 34-35 are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

CLAIMS 26, 28-29, 31, 34-36, 42-55 and 75-94 ARE PENDING IN THE INSTANT APPLICATION

Response to Amendment

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's arguments filed 16 January 1996 have been fully considered but they are not all deemed to be persuasive.

2. Claim 88 does not comply with 37 CFR 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence. The sequence of claim is not part of the original CRF, therefore an amended CRF containing said sequence must be submitted. See M.P.E.P. 2422.04.

3. The following rejections have been withdrawn in response to applicants' amendments or rebuttals:

Claims 26, 28-29, 31, 34-36 and 42-55 were rejected for the reasons of record. Applicants' positions, except those regarding hybridization and homology language (see below) are deemed persuasive.

Applicants' cancellation of claim 36 and amendment of all other pending claims regarding the objection of record of this claim due to its use of the term "dopaminergic activity" is noted and the rejection of record withdrawn.

Applicants' amendment of claim 44 to remove the phrase "conditions of amplification of the vector" is noted and the rejection is withdrawn.

Claims 28, 31, 35-36 were rejected under USC § 112 2nd paragraph, were rejected for being indefinite as to which sequences the claims of record were drawn, the rejection of record under USC § 112 2nd paragraph is withdrawn.

The following rejections have been made in response to Applicants' amendments:

4. 35 USC § 112 - 1st paragraph:

Claims 26, 31, 36, 42-55, 75-87 and 89-94 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the disclosed sequences referred to by specific SEQ ID NOs.

The disclosure is only enabling for the disclosed *GDNF* nucleic acid sequences identified specifically (e.g. in claim 26, SEQ ID NOs 3, 4, 6). In so far as the instant claims encompass a *GDNF* sequence encoded by a gene which has yet to be cloned,

specific case law bears on this issue: Amgen Inc. V. Chugai Pharmaceuticals Co. Ltd, 18 U.S.P.Q. 2d, 1016, held that:

"A gene is chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and describe how to obtain it. See OKA 849 F.2d at 583, 7 USPQ 2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by it's method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, e.g., encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e. until after the gene has been isolated"

Hence claims reciting the term "homologous" are not enabling and are rejected under 112 first paragraph. Support for the phrases "homologous," "at least 70 percent homologous," "at least 90% homologous" is not commensurate with the scope of the claims. The specification does not provide guidence as to how to compute "homology" nor is there an accepted single definition available from teachings in the art of the invention, hence, the metes and bounds of "calculating" homology are not defined in claims as written; no do they define what is included or what is excluded from the invention. The instant specification does not enable an artisan to make an *GDNF* protein homologous to the disclosed SEQ ID NOs because it does not identify those amino acid residues (or base pairs of the NA encoding the recombinant protein(s)) in the amino acid sequence of *GDNF* which are essential for its

biological activity and structural integrity and those residues which are either expendable or substitutable. Further, no examples or guidance to make specific sequences are cited that would enable a skilled artisan to produce a homologous recombinant *GDNF* protein having the biological activity of *GDNF*, nor are there sufficient prior art teachings to enable one skilled in the art to produce such a peptide, which precludes one from reasonably predicting the result of different modifications to the peptide sequence without an inordinate degree of experimentation. In the absence of this information, a practitioner would have to resort to a substantial amount of undue experimentation in the form of insertional, deletional and substitutional mutation analysis of over 200 amino acid residues before they could even begin to rationally design a functional *GDNF* having other than a natural amino acid sequence.

The aforementioned analysis is equally applicable in claims 26 parts d and e and claim 31 part c and d which use the language or phrases "hybridize" or "sequence which...would hybridize..." The disclosure of a single DNA sequence encoding a single *GDNF* with a natural amino acid sequence is clearly insufficient to support under the first paragraph of 35 U.S.C. § 112 for claims which encompass any and all *GDNF* proteins, including mutants thereof, which are encoded by a DNA which hybridizes to a DNA having only the disclosed sequence under condition of hybridization which are not defined in the specification. The

claims must adequately delimit the metes and bounds of what the applicant deems the invention to be and such relative terminology, is insufficient to enable one of ordinary skill in the art to make or use the claimed invention. Given that there are hybridization conditions whereby any DNA will hybridize to any other DNA without specificity, the specification does not provide an example of specific stringency parameters nor a definition of what the applicant considers the term hybridization to delimit. The specification does not support such an invention in: teachings in the art of record, in recitations of the state of the prior art; nor is there recitation of examples or other guidence present in the specification to enable such procedures, and because of these deficiencies one of ordinary skill in the art would have no reasonable means of predicting the outcome of an undefined hybridization conditions referred to ambiguously as "reduced stringency" nor be able to obtain the results claimed without undue experimentation. See M.P.E.P. § 706.03(n) and 706.03(z).

Claims 20 ~~36~~(e) and 87 are also rejected for the aforementioned reasons in that the claim as drafted again recites no specific nucleic acid or encoded protein by SEQ ID NO, but failing to do so, as drafted reads on any protein with the recited biologic activity (e.g. "...stimulates dopamine uptake in dopaminergic neurons..."; "...bound by an antibody which binds an amino acid sequence..."). Hence claim reads on any protein that can

generate the recited activity and could be bound by a broad spectrum antibody. Applicant does not identify a specific antibody, nor provide evidence that such an antibody would be specific for SEQ ID NOs 4 or 6 but at the same time NOT bind any other proteins. Again, the specification does not support such an invention in: teachings in the art of record, in recitations of the state of the prior art; nor is there recitation of examples or other guidence present in the specification to enable such procedures, and because of these deficiencies one of ordinary skill in the art would have no reasonable means of predicting how to generate an antibody with the recited activity which also encompassed the other limitations in the claim as drafted without undue experimentation. Thus it would constitute undue experimentation to practice the instant invention as claimed. See M.P.E.P. §§ 706.03(n) and 706.03(z).

5. 35 USC § 112 2nd paragraph:

Claims 26, 31, 42-55, 75-87, 89-94 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims use the language "at least 70% homologous," or "at least 90% homologous." The phrases employing the term "homologous" are vague and indefinite because no precise definition is recited for what constitutes "homologous" in the

body of the specification and the applicant does not clearly teach or refer to any means for obtaining "homologous" sequences to *GDNF*. Because the term "homologous" does not have an accepted definition to one skilled in the art it is important for the applicant to clearly delimit this term on which the claims. The ambiguity of "homology" or "homologous" is best shown by example: consider the two sequences ABCDEF and ABEF. These could be compared in any of four ways:

```
ABCDEF    4/6 = 67%
II
AB--EF    4/4 = 100%

ABEF      2/4 = 50%
II
ABCDEF    2/6 = 33%
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Thus it is unclear which sequences the claims encompass. Hence, the claim is therefore uninterpretable as to the delimits of the sequences the applicant intends to claim as the invention.

Claims 26 and 31 use improper Markush language; claim should be drafted with conjunctive rather than alternative language (e.g. "...selected from the group consisting of A,B, **AND** C"). Claims as drafted do not follow this form.

Claims 28-29, 34-35, are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 88 is allowable as drafted.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kenneth A. Sorensen at telephone number (703) 305-5377. The examiner can normally be reached on Monday through Friday from 9:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Stephen Walsh can be reached on (703) 308-4232. The FAX phone number for this group is (703)308-0294.

Any inquiry of general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Marianne P. Allen

MARIANNE P. ALLEN
PRIMARY EXAMINER
GROUP 1800

Kenneth A. Sorensen

Examiner